JOC Article

1,5-Anti Stereocontrol in the Boron-Mediated Aldol Reactions of β-Alkoxy Methyl Ketones: The Role of the Formyl Hydrogen Bond

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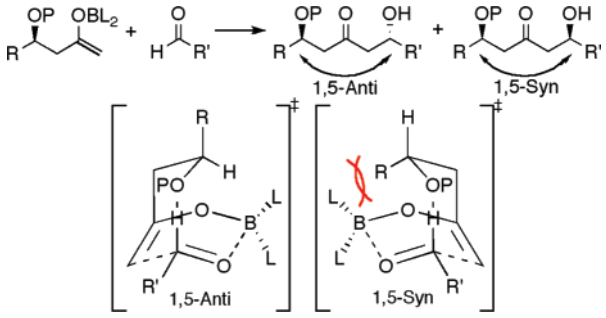

The boron-mediated aldol reactions of certain types of β-alkoxy methyl ketone show remarkably high levels of stereoinduction with achiral aldehydes, leading preferentially to 1,5-anti related stereocenters. Given the low levels of asymmetric induction usually observed in acetate aldol reactions, this is of great synthetic utility and has been used successfully in the total synthesis of a number of polyketide natural products. We have investigated the effects of the alkoxy protecting group (OMe, OPMB, PMP acetal, tetrahydropyran, and OTBS) present in the boron enolate on the level and sense of remote 1,5-stereoinduction, using density functional theory calculations (B3LYP/6-31G**). Our predictions of diastereoselectivity from comparison of the competing aldol transition structures are in excellent qualitative and quantitative agreement with experimentally reported values. We conclude that the boron aldol reactions of unsubstituted boron enolates proceed via boat-shaped transition structures in which a stabilizing formyl hydrogen bond exists between the alkoxy oxygen and the aldehyde proton. It is this interaction that leads to preferential formation of the 1,5-anti adduct, by minimizing steric interactions between the β-alkyl group and one of the ligands on boron. In the case of silyl ethers, the preference for this internal hydrogen bond is not observed due to the size of the protecting group and the electron-poor oxygen atom that donates electron density into the adjacent silicon atom. We show that this stereochemical model is also applicable in rationalizing the 1,4-syn stereoselectivity of boron aldol reactions involving certain α-chiral methyl ketones. These detailed results may be summarized as a conformational diagram that can be used to predict the sense of stereoinduction.

Introduction

The aldol reaction allows the construction of new carbon−carbon bonds in a regio-, diastereo-, and enantioselective manner.[1] The kinetically controlled, boron-mediated aldol reaction is particularly powerful for the efficient synthesis of β-hydroxy carbonyl compounds.[2] Compared to other metal enolates, the boron−oxygen bond in boron enolates is relatively short which, on addition to aldehydes, leads to tight cyclic transition states and highly stereoselective carbon−carbon bond formation. The ability to achieve such highly controlled aldol bond assemblies using boron enolates enables their application to the synthesis of the carbon and oxygen skeleton of stereochemically rich, polyol-containing, natural products.[3] In particular, the polyketides represent a diverse array of structurally complex natural products having a wide range of important biological activities. Due to their low natural abundance coupled with the unsustainable ecological impact of large-scale isolation, detailed biological evaluation (and possible clinical development) of marine-derived polyketides is possible only following total synthesis. In this arena, synthesis is also important for

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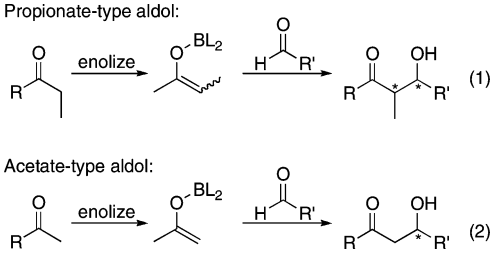
structural elucidation, including determination of the full absolute configuration, often leading to a structural or stereochemical reassignment.[4] Moreover, the synthetic route has to meet the major challenge of being practical enough to deliver sufficient quantities of pure materials to permit preclinical and possibly clinical testing as well as being flexible enough for structural diversification to access analogues for SAR studies.

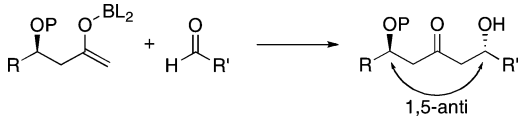
Asymmetric aldol reactions of boron enolates with a wide range of aldehydes (prochiral or chiral) give ready access to elaborate segments of polyketide natural products in an efficient manner. Control over relative and absolute stereochemistry can be achieved using chiral auxiliaries attached to the boron enolate, such as Evans oxazolidinone auxiliaries,[5] or chiral ligands on boron and the inherent stereocontrol provided by chiral substrate(s). In cases where the underlying substrate control is moderate, the use of ligand or auxiliary control can be employed in a matched sense to enhance the stereoselectivity, or in a mismatched sense to overturn the substrate selectivity.[6] Such controlled asymmetric boron-mediated aldol reactions have emerged as especially powerful tools for the efficient installation of the characteristic stereochemical arrays of alternating methyl and hydroxy groups. Subsequent elaboration of the corresponding β-hydroxy ketone adducts can then be performed with a high level of overall diastereoselectivity. For example, carbonyl reduction can be realized by appropriate choice of reagent to produce 1,3-syn[7] or 1,3-anti[8] diols selectively.

Aldol reactions can be categorized into two major families based on the structure of the enolate component. The first type involves the use of enolates bearing α-substituents. Most often, the α-substituent is a methyl group, and this class is termed "propionate-type" aldol reactions (Scheme 1, eq 1). Aldol reactions using simple enolates lacking an α-substituent are called "acetate-type" aldols (Scheme 1, eq 2). This classification is useful because propionate-type aldol reactions and acetate-type aldol reactions exhibit different behavior in asymmetric systems. In contrast to the highly enantioselective reactions of ethyl ketones with chiral isopinocampheyl (Ipc) ligands on boron, methyl ketones exhibit only modest enantioselectivity in the opposite sense.[9] Likewise, boron-mediated acetate-type aldol reactions employing chiral oxazolidinone auxiliaries show low levels of diastereoselectivity.[10] The contrasting stereochemical behavior of methyl and ethyl ketones can be attributed to the preference of propionate-type aldol reactions to proceed *via* chair-shaped transition structures, while acetate-type aldol reactions proceed *via* boat-shaped transition structures.[11] Hence, asymmetric acetate-type aldol reactions have been utilized much less frequently in the total syntheses of natural products than propionate-type aldol reactions, due to the generally lower stereoselectivities.

SCHEME 1. Classification of Aldol Reactions According to Enolate Type



SCHEME 2. 1,5-Anti Selectivity of Unsubstituted Enolates Bearing a Protected β-Hydroxyl Stereocenter



Due to the lack of stereoselectivity with chiral auxiliaries and chiral ligands, reagent control is necessary to obtain synthetically useful levels of asymmetric induction in the addition of unsubstituted boron enolates to achiral aldehydes.[12] Paterson[13] and Evans[14] have reported a quite remarkable case of stereoinduction that occurs in the reactions of β-alkoxy methyl ketones, which gives rise to the 1,5-anti aldol adduct with high levels of diastereoselectivity in the absence of chiral ligands and auxiliaries (Scheme 2).

The β-hydroxy ketones thus obtained may be reduced in a controlled fashion, leading to the efficient synthesis of long-chain 1,3-polyols. This Evans−Paterson substrate-controlled 1,5-

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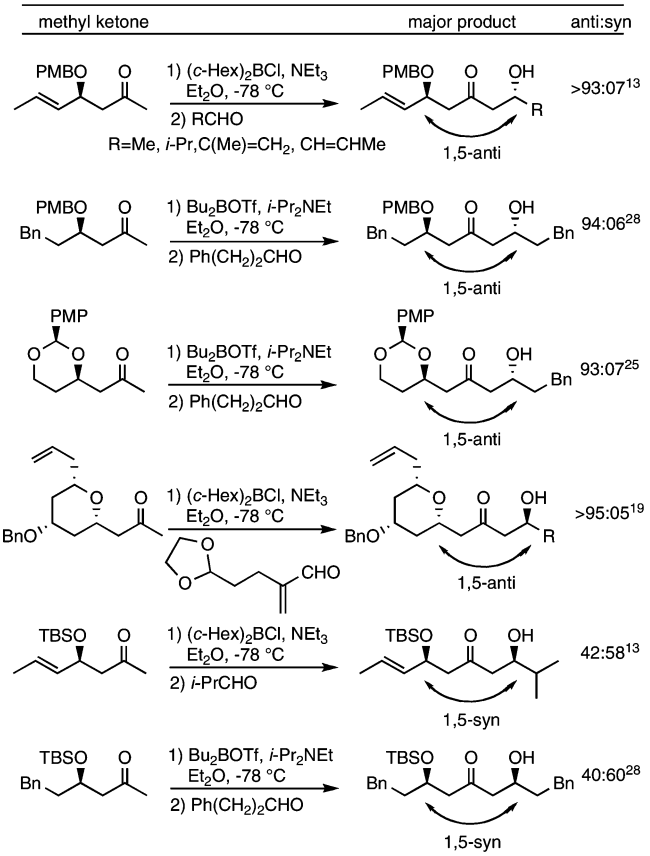
SCHEME 3. Boron Aldol Reactions of β-Alkoxy Methyl Ketones; PMB Ethers, PMP Acetals, and Tetrahydropyrans Show High 1,5-Anti Induction; Silyl Ethers Show Poor Selectivity



anti aldol methodology has been employed in the total synthesis of many polyketide natural products including phorboxazole B,[15] roxaticin,[16] discodermolide,[17] peloruside A,[18] leucascandrolide A,[19−21] spongistatin 1,[22,23] dolabelide D,[24] and oasomycin A[25] and in studies toward the synthesis of reidispongiolide A.[26]

Scheme 3 outlines some characteristic results obtained for boron-mediated aldol reactions involving methyl ketones with a variety of commonly used hydroxyl protecting groups at the β-position. High levels of 1,5-induction are obtained with benzyloxy, benzylidene acetal, and tetrahydropyran protecting groups at the β-position, whereas silyloxy groups give rise to little or no selectivity. It is, nevertheless, possible to achieve higher levels of stereocontrol through the reinforcing influence of an Ipc-substituted boron enolate.[7,27] It is likely that electronic rather than steric effects are responsible for the enolate face selectivity and that the nature of the β-oxygen protecting group is critical in determining the level of induction. This is consistent with high 1,5-anti selectivity observed for β-substituents of a similar steric size but differing in their electronic properties (−OCH_2Ar vs −CH_2CH_2Ar, Scheme 3, entry 2) and the observation that a decrease in solvent polarity results in higher selectivity.[28] A π-stacking interaction between aromatic protecting groups and the C═C of the boron enolate has been proposed to play a role in the cyclic aldol transition state.[29] However, this model cannot account for 1,5-anti selectivity where both β-substituents possess aromatic groups (−OCH_2Ar vs −CH_2CH_2Ar, Scheme 3, entry 2), nor why the example −CH_2CH_2Ar vs −OTBS (Scheme 1, entry 6) is unselective despite the presence of an aromatic substituent. These results suggest that it is the electronic properties of the β-oxygen that are essential for 1,5-stereocontrol. Protecting groups lacking an aromatic group such as the tetrahydropyran (Scheme 1, entry 4) have been used to give very high levels of 1,5-anti selectivity, and even β-methoxy groups are observed to give rise to moderate levels of 1,5-anti selectivity.

Theoretical Design

The objective of this study is to determine the structural and electronic features of various commonly used hydroxyl protecting groups that are responsible for this remarkable case of remote stereoinduction. A full understanding of the electronic and steric requirements of the alkoxy group is required, as this knowledge can be used to decide protecting group strategies, which can be designed to take advantage of and maximize this substrate-controlled stereoinduction. Since the boron aldol reaction is performed under conditions of kinetic control, such an analysis can be performed from a comparison of the competing boron aldol transition structures, because this is the irreversible step in which the new stereocenter is formed. Calculations were performed using density functional theory (DFT) since this method has been shown to give results that are in excellent agreement with experiment in numerous computational studies. Typically, cyclohexyl or *n*-butyl ligands on boron are used experimentally. However, in our investigation, methyl groups were chosen to make the computations tractable. We reported in an earlier communication[30] that this computational methodology has performed well in providing predictions of diastereoselectivity that are in line with experimental values.

Computational Methods

All calculations were carried out using the *Jaguar 6.0* computational chemistry package.[31] All species have been fully geometry optimized, and the Cartesian coordinates are supplied in the

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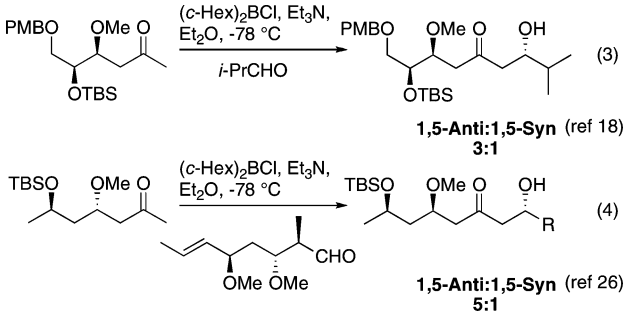
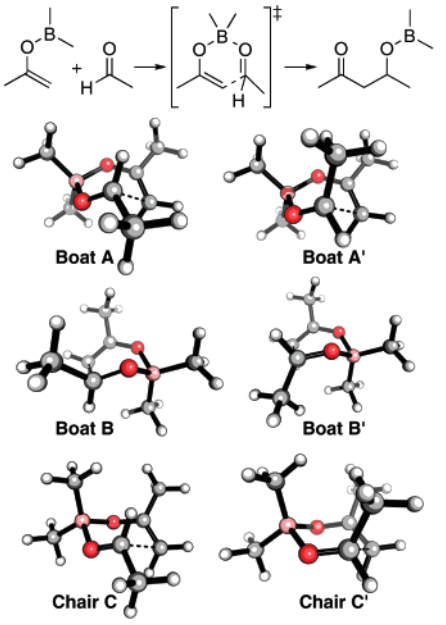
Supporting Information. For all transition structures, standard convergence parameters within Jaguar (which correspond to R.M.S. gradients below 0.0003 hartrees/bohr) have been used. The well-established B3LYP density functional[32] was used in combination with the split-valence polarized 6-31G** basis set.[33] This decision is supported by a recent theoretical study of boron aldol transition states by Evans and Cramer[34] which showed that the relative energies were consistent with respect to different combinations of basis sets, concluding that B3LYP/6-31G* does not suffer from any deficiencies relative to (more expensive) calculations performed using second-order perturbation theory (MP2).[35] A medium grid density was used throughout. All transition structures were obtained by unconstrained optimization, and frequency calculations have been performed to check for the presence of a single imaginary frequency. The corresponding eigenvector was carefully inspected within the visualization program *Molden*[36] to confirm that it did indeed correspond to the expected reaction coordinate: a forming carbon−carbon bond in an aldol reaction. The reaction coordinate was explicitly calculated using QRC[37] for the reaction of the dimethyl boron enolate of acetone with ethanal, connecting each transition state with an ate-complex and an aldolate adduct, and fully confirming that the transition structures we have located are for the aldol reaction. NBO delocalization energies were calculated using second-order perturbation theory with the *NBO 4.0* program[38] as implemented in *Jaguar 6.0*. Zero-point energies were determined from vibrational frequency analysis (imaginary frequencies are neglected) and are included in the reported gas-phase energies. Predicted diastereomeric ratios were calculated from Boltzmann factors evaluated from the relative energies at the standard reaction temperature of −78 °C.

In our comparison of the competing transition structures, the effects of solvation on the relative energies are evaluated using the polarizable continuum−Poisson method as implemented in *Jaguar*.[39] The solvent accessible molecular surface was defined by atomic van der Waals radii optimized to reproduce accurate solvation energies of a data set of neutral molecules. Single-point calculations were performed on the gas-phase optimized geometries in each case. The justification for this approach was provided by a preliminary study of the boron aldol reaction between acetone and ethanal (eq 3).



Relative energies for the transition structures were evaluated, first by optimization in the gas-phase, second by full optimization using a polarizable continuum model of diethyl ether[40] and finally, by a single-point calculation in ether performed on the gas-phase optimized geometry. Single-point solvation energies were in good agreement with those obtained from a full optimization in solvent, and the geometries were almost identical (Figure 1). That the effects of solvation do not significantly alter the geometries is to be expected, given the apolar nature of the cyclic transition structure. Therefore, the additional computational cost of full geometry optimization in solvent was deemed unnecessary. Nevertheless, we felt that a consideration of solvation was important in our study of alkoxy ketones since the polar C−O bond should interact favorably with solvent. Omission of this treatment may well lead to the exaggeration of any intramolecular electrostatic interactions, which are attenuated by the presence of solvent.



TS	optimization in vacuum	optimization in Et_2O	single point in Et_2O
A	0.00	0.00	0.00
A'	3.02	2.70	3.14
B	0.82	0.93	0.58
B'	5.01	4.95	5.66
C	1.86	1.46	1.46
C'	6.60	5.99	6.18

FIGURE 1. Transition structures for the reaction between a dimethyl boron enolate of acetone and ethanal (relative energies in kcal mol^{-1}).

Results and Discussion

Simple Aldol Transition Structures. The competing transition structures for the aldol reaction between acetone and ethanal (eq 3) were investigated and are shown below in Figure 1. As

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(35) It was found that calculated barrier heights to rotation were twice experimental values. However, there was excellent agreement in conformational relative energies calculated at both B3LYP and MP2 level, which is relevant to our study.

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(40) A dielectric constant of 4.27 and a probe radius of 3.21913 Å taken from the *CRC Handbook of Chemistry and Physics*, 85th ed. (CRC Press: Boca Raton, FL, 2004/2005) were used to describe one of the most commonly used solvents, diethyl ether.

has been reported previously by Houk[41] and Bernardi[42] for the aldol reaction using only hydrogen substituents, at the HF/3-21G level of theory, there are three possible geometries for the cyclic aldol transition structure: a chair and two distinct boat geometries, herein referred to as boat A, boat B, and chair C. Each of these ring geometries further gives rise to two distinct transition structures that differ only in the orientation of the aldehyde, leading to six possible aldol transition structures. Unsurprisingly, those with the aldehyde substituent in a pseudo-equatorial environment (Boat A, Boat B, and Chair) are lower in energy than their counterparts with a pseudoaxially disposed aldehyde substituent (Boat A′, Boat B′, and Chair′) as they minimize unfavorable steric interactions.

The boat-like transition structures are energetically more favorable largely because they avoid the 1,3 diaxial interaction between ligand and enolate side chain present in the chair structure. Boat A is energetically most favored and also the latest of the transition states, with the shortest forming C−C distance of 2.362 Å. At −78 °C, boat A is most populated (88.7%), while boat B (10.6%) is marginally populated. Chair C (0.7%) is hardly populated at all and has little impact on the boron-mediated aldol reaction of methyl ketones. Calculations performed at the same level of theory on ethyl ketones reacting with ethanal[11] reveal that in these boron-aldol reactions the chair TS is much more important. Indeed, it is the marked preference for a boat-shaped TS that gives rise to the contrasting examples of stereoinduction (or lack of it) in the reactions of methyl ketones. The effect of solvation has a small impact on the relative energies and does not alter the order of stability. This is to be expected because the solvent accessible surface area of each structure is of a similar size, and there are no highly charged regions which will have particularly strong electrostatic interactions with the relatively apolar, aprotic solvent diethyl ether (dielectric constant 4.25).

Alkoxy Methyl Ketones. It is not obvious from the above analysis why a distant stereogenic center on the enolate component of the reaction should have such a strong effect on the stereochemical outcome. The next step therefore, was to study competing transition structures for the reaction of the boron enolate of a simple achiral β-alkoxy methyl ketone with ethanal. We considered all those structures based on boat A and the chair C arising from a rotation about the two extra-annular bonds of the enolate alkyl chain. Of the 18 possible structures generated some of the hypothetical rotamers are inherently unstable due to severe steric repulsions. All those successfully optimized are detailed in full in the Supporting Information (Table S1), while the low-energy transition structures are depicted in Figure 2. We label these structures A for boat-A, C for Chair, and "In" and "Out" to signify whether the methoxymethylene chain points in toward the approaching aldehyde, or out and away from the aldehyde.

As before, boat A-shaped transition structures are found to be energetically favored in the boron-aldol reactions of methyl ketones. Rotation of the extra-annular bonds so that the CH_2-CH_2OCH_3 side chain of the enolate is oriented away from the approaching aldehyde is expected to alleviate unfavorable steric interactions, as seen in the transition structures (**A-Out**) and (**C-Out**). However, these are not the most energetically favorable conformations. Interestingly, in the most stable conformation (**A-In**) the alkoxy side chain is folded toward the approaching aldehyde and the forming C−C bond. On purely steric grounds this is an unexpected result. However, we note the very short distance (2.355 Å) between the methoxy-oxygen and formyl-proton. We suggest, therefore, that there is a favorable formyl-hydrogen bonding (C−H−O) interaction between the two atoms, a concept previously explored in boron Lewis acids by Corey[43] and ourselves.[44] The Paterson group has previously proposed this working model of 1,5-anti induction via an internal formyl hydrogen-bond.[45] A related formyl hydrogen-bond argument has been also used by Paterson to rationalize the high stereoselectivity observed in the boron aldol reactions of certain α-acyloxy ketones.[46] The magnitude of this interaction was assessed by natural bond order (NBO) analysis[47] of the optimized structures. The energy associated with oxygen lone pair donation into the C−H σ^* is 3.17 kcal mol^{-1},[48] and there is a resultant increase in the electronic occupancy of the C−H σ^* orbital. In comparison, formyl hydrogen bonding in boron Lewis acids has been previously calculated to confer 2.2 kcal mol^{-1} of stability at the MP2/6-31G** level.[44] The same favorable interaction is possible in the chair structure, although the C−H−O separation is greater and was calculated to provide only 0.91 kcal mol^{-1} of stabilization. The extent of delocalization in the chair is less pronounced because in achieving a close

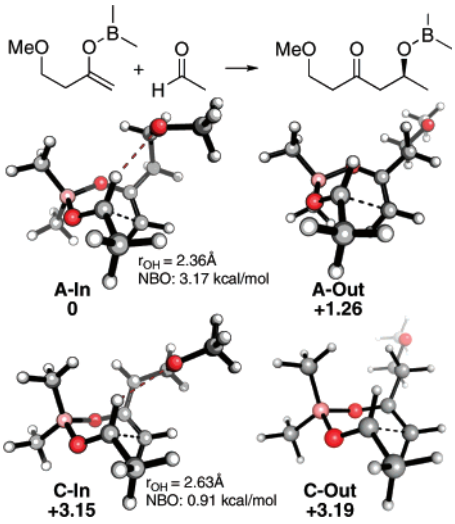


FIGURE 2. Competing transition structures for the boron aldol reaction of an achiral β-methoxy methyl ketone with ethanal (relative energy in kcal mol^{-1} calculated in Et_2O).

(41) (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684−3687. (b) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493.

(42) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576−3581.

(43) (a) Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38*, 33−36. (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37−40. (c) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1977**, *38*, 1699−1702.

(44) (a) Mackey, M. D.; Goodman, J. M. *Chem. Commun.* **1997**, 2383−2384. (b) Brodbelt, J. S.; Isbell, J.; Goodman, J. M.; Secor, H. V.; Seeman, J. I. *Tetrahedron Lett.* **2001**, *42*, 6949−6952.

(45) Paterson, I. University of Cambridge, personal communication; Coster, M. Ph.D. Thesis. University of Cambridge, 2001.

(46) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652.

(47) Weinhold, F. In *Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Ed.; Wiley: New York, 1998; pp 1792−1811.

(48) Donor−acceptor interactions are computed according to the equation: $\Delta E^{(2)}_{\phi\phi^*} = -2(\langle\phi|\hat{F}|\phi^*\rangle)/(\epsilon_{\phi^*} - \epsilon_{\phi})$ where $\hat{F}$ is the Fock operator and ϕ and ϕ^* are two filled and unfilled NBOs having ϵ_{ϕ} and ϵ_{ϕ^*} energies, respectively.

(49) Paterson, I.; Findlay, A. D.; Florence, G. J. *Org. Lett.* **2006**, *8*, 2131−2134.

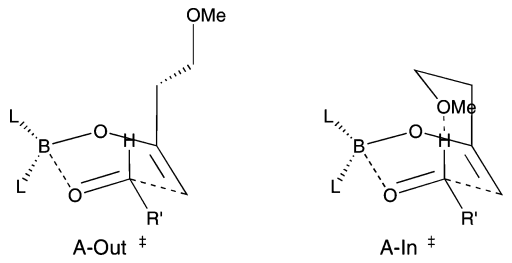


FIGURE 3. Boat transition structures in competition.

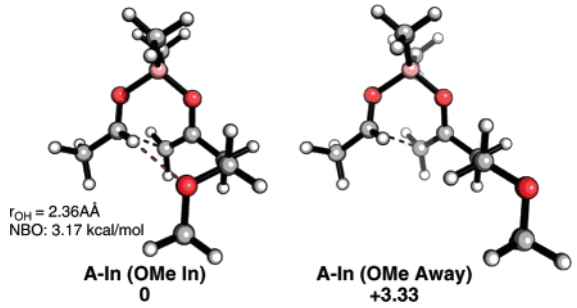


FIGURE 4. Boat transition structures differing in orientation of methoxy group (relative energy in kcal mol^{-1} calculated in Et_2O).

C−H−O contact the β-carbon eclipses the enolate double bond resulting in allylic 1,3-strain. In both of the boat-shaped conformers the double bond is eclipsed by hydrogen and they remain more favorable than the chair (Figure 3).

Folding the alkyl chain toward the approaching aldehyde is sterically unfavorable but the stabilizing C−H−O interaction more than compensates for this. Therefore, we expect to see an increase in energy as this distance is increased. This is exactly what is observed, and in the absence of a short C−H−O distance, the transition structure is higher in energy when the alkyl group is pointing back inside. The difference in energy between the transition structures in Figure 4 can be rationalized by taking into account the calculated NBO delocalization energy that stabilizes the favored structure by 3.3 kcal mol^{-1}. It is worth noting that the dipolar arrangement of the two conformers is very similar, so the energetic contribution from dipolar repulsion/attraction will be approximately identical for each structure. Finally, we note that our formyl−hydrogen bond postulate is also consistent with the experimental observation that 1,5-anti diastereoselectivity is lower in dichloromethane than diethyl ether,[28] since it is expected that the more polar solvent would attenuate any electrostatic interaction between the formyl hydrogen and the alkoxy oxygen.

This analysis can be reduced to a simple working model (Figure 5). The formyl hydrogen bond is part of a seven-membered ring with the enolate and the forming C−C bond of the aldol reaction. We draw this schematically, reducing the C−H−O hydrogen bond to a single bond in a chair seven-membered ring, fused to the boat six-membered ring of the aldol transition state. This model illustrates how the small and large groups in the β-position control the stereochemistry of the product. On the basis of this model, we expect the α-position to have less of an effect.

The effect of the formyl hydrogen bond on the activation energy of the boron aldol reaction was considered. Relative to an enolate lacking a β-alkoxy substituent, the activation energy (starting from the separate enolate and aldehyde) is lowered by 4.0 kcal mol^{-1} for a β-methoxy ketone with a formyl H-bonding

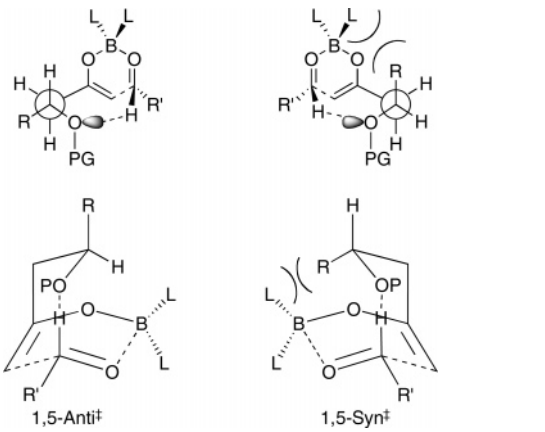


FIGURE 5. Diastereomeric 1,5-anti and 1,5-syn transition structures, with the unfavorable steric clash highlighted in the 1,5-syn TS.

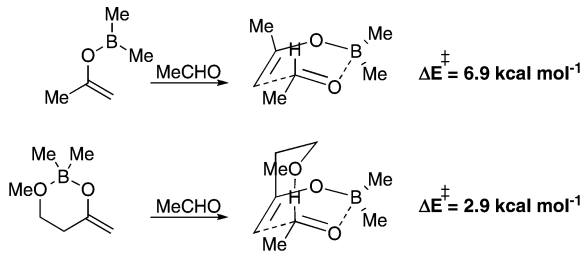


FIGURE 6. Activation energies with and without formyl H-bonding.

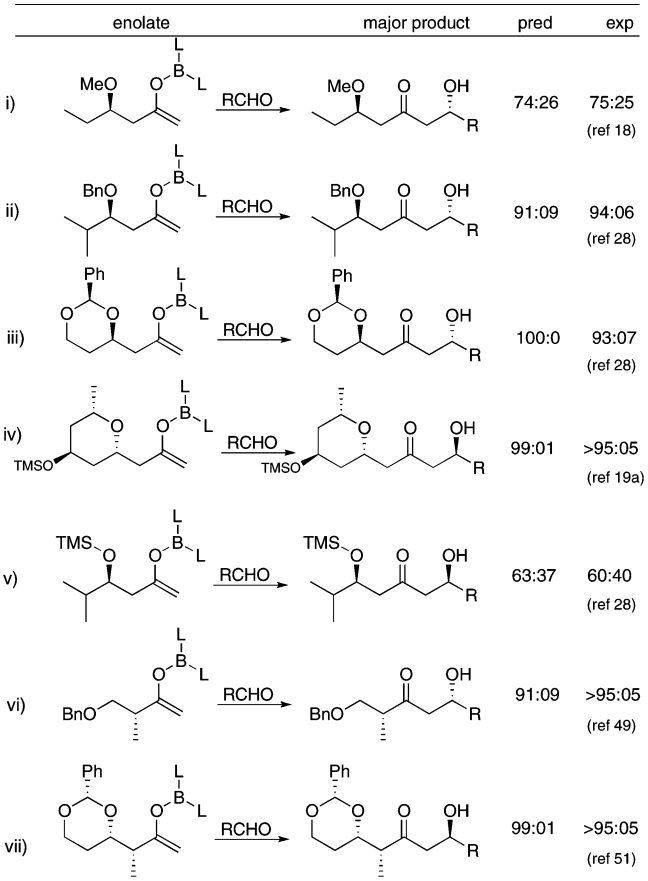
interaction present (Figure 6). We also considered the effect that deuteration of the formyl hydrogen would have on the preference for a formyl hydrogen bond: the preference of the A-In transition structure relative to A-Out is increased by only 0.1 kcal mol^{-1}.

We also investigated the boron aldol transition structures for the analogous reaction of a γ-methoxy methyl ketone with ethanal to determine if there exists a similar preference for internal hydrogen bond formation. As before, we were able to optimize transition structures (shown in the Supporting Information, Figure S1) in which the enolate side chain is folded away from, and also toward the approaching aldehyde, establishing a short C−H−O distance. Unlike the β-methoxy ketone, however, there is no energetic preference for the folded back transition structure (indeed it is disfavored by 1.5 kcal mol^{-1}). Given this energetic preference for a more open, less organized, transition structure we expect there to be little potential for diastereomeric discrimination were there any stereogenic centers present in the enolate. On this basis we predict that remote 1,6-stereoinduction due to a γ-alkoxy group will be insignificant in comparison to 1,5-stereoinduction, in the absence of further functionalization of the chain.

Examples. We have investigated a series of reactions for which experimental data is available, testing both the density functional analysis, which we expect to give quantitatively accurate results, and the predictive model transition state, which should give the correct qualitative picture. The predicted diastereoselectivities are tabulated in Scheme 4. We have compared our predictions with closely related experimental reactions, which are explained fully in this text.

Only boat-like transition structures were considered for the larger model studies, since based on the results obtained for the achiral reaction outlined above, we expect that chairlike

SCHEME 4. Predictions of Selectivity from Our Calculations; in Our Model Computational Systems Investigated L = Me and R=Me; These Are Compared with Experimental Values for Structurally Related Reactions That Are Described in the Text



transition structures are insignificantly populated at the standard reaction temperature of −78 °C.

***β*-Methoxy-Substituted Methyl Ketones** (Scheme 4, entry i). Moderate selectivity in preference of the 1,5-anti adduct is observed in reactions where a *β*-methoxy group is present (eqs 3 and 4). Reacting with an achiral aldehyde gives 3:1 selectivity in favor of the 1,5-anti adduct, while additional Felkin−Anh control derived from a chiral aldehyde favoring the 1,5-anti adduct is seen to bolster the level of selectivity to 5:1. The presence of additional stereocenters in the enolates will have an effect; although, since they are further away than the *β*-stereocenter, we expect this to be less important than the methoxy group.

Anti and syn transition structures based on boat A were generated by rotations around the extra-annular bonds (see Supporting Information for full details), and a summary of the low-energy structures is presented in Figure 7. A comparison of the transition structures in which the methoxy group is oriented toward the approaching aldehyde (**In-Anti** and **In-Syn**) and those in which the enolate side chain is fully extended away from the approaching aldehyde (**Out-Anti** and **Out-Syn**) reveals an energetic preference for a short distance between the methoxy oxygen and the formyl hydrogen. This stabilizing formyl H-bond interaction can occur in two diastereomeric transition structures, **In-Anti** and **In-Syn,** of which the former (leading to the 1,5-anti adduct) is preferred.

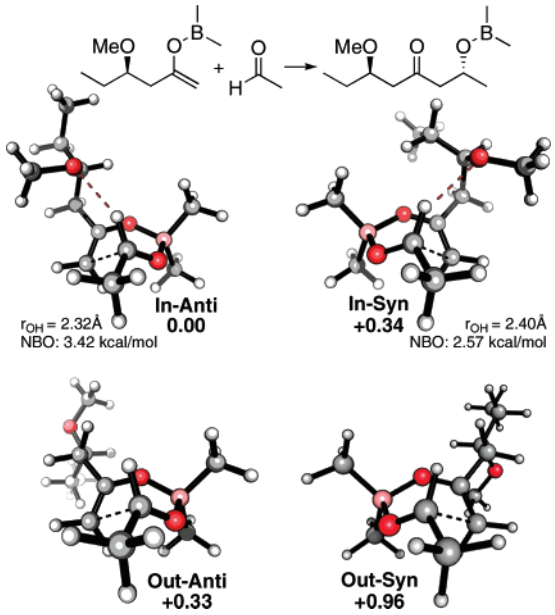


FIGURE 7. Aldol transition structures for a *β*-methoxy methyl ketone reacting with ethanal (relative energy in kcal mol^{-1} calculated in Et_2O).

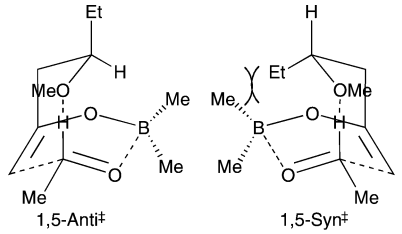
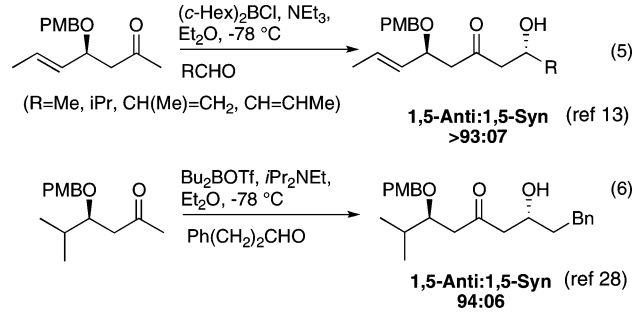


FIGURE 8. Diastereomeric 1,5-anti and 1,5-syn transition structures, with unfavorable steric clash highlighted in the 1,5-syn TS.

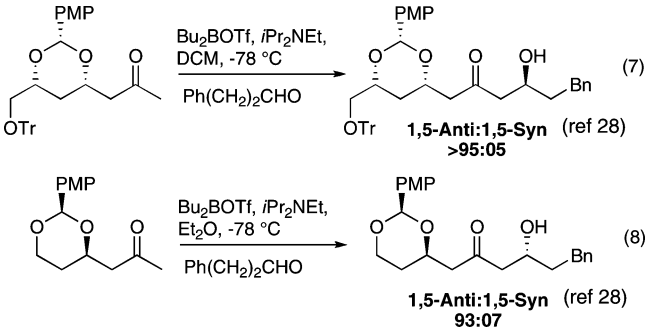
The 1,5-anti transition structure is favored since in the competing 1,5-syn transition structure the *β*-alkyl group is oriented toward one of the ligands on boron, leading to an additional steric repulsion. This fits the qualitative picture presented in Figure 5. This particular example is drawn in Figure 8. This in turn leads to a longer O−H distance in the 1,5-syn than in the 1,5-anti transition structure (2.396 vs 2.322 Å) and, consequently, to a smaller delocalization energy (2.57 vs 3.42 kcal mol^{-1}) calculated by the NBO method. The relative energies of the transition structures shown predict a 1,5-anti to 1,5-syn ratio at −78 °C of 74:26 (based on all transition structures detailed in the Supporting Information this ratio is 80:20), which is in rather good agreement with the reported ratios of 3:1 and 5:1 (eqs 3 and 4), although we have not investigated the effects of the more remote stereocenters in the enolate. We expect these more remote stereocenters to play a role in influencing the stereochemical outcome, but a smaller one than that of the *β*-stereocenter. Hence, for reasons of computational tractability, these very distant effects are not studied here.

***β*-Benzylic Ether-Substituted Methyl Ketones** (Scheme 4, entry ii)**.** Parmethoxybenzyl (PMB) protecting groups at the *β*-hydroxy position are commonly used since they give rise to excellent levels of remote 1,5-anti induction (eqs 5 and 6) and are easily removed under oxidative conditions. For a wide range of achiral aldehydes *β*-OPMB-substituted methyl ketones give levels of 1,5-anti stereoinduction consistently in excess of 93:07.



Transition structures were calculated for a model system in which the PMB group is replaced with a benzyl group and are shown in full in the Supporting Information (Figure S2). As before, a short C−H−O distance is favored, in structures **In-Anti** and **In-Syn**. Again, steric repulsions between the β-alkyl substituent and one of the ligands on boron are minimized in the transition structure leading to the 1,5-anti adduct. In accordance with experiment, reactions with a β-OPMB group are predicted to be more selective than a β-methoxy group, with the In-Anti transition structure favored by 1.0 kcal mol^{-1} relative to the In-Syn structure. The CH−O distance is very similar in both cases, and the difference arises from a greater preference for the In-TS in the β-OPMB case. This may be due to a favorable interaction between the aromatic group and the core of the transition structure. The reaction pathway via these well-organized transition structures (rather than through the competing, less compact, transition structures) gives rise to high levels of diastereomeric discrimination. The relative energies predict a 1,5-anti to 1,5-syn ratio at −78 °C of 91:09, which is in excellent agreement with the observed values of 93:07 or greater.

***β*-Benzylidene Acetal-Substituted Methyl Ketones** (Scheme 4, entry iii). Like PMB ethers, a β-hydroxy group protected as a cyclic benzylidene or para-methoxyphenyl (PMP) acetal gives rise to high 1,5-anti induction (eqs 7 and 8).



Since the substituents of the six-membered acetal ring prefer to occupy equatorial positions (particularly in the trisubstituted example in eq 7), the possibility of an interaction between the aromatic and C−C π-bond of the enolate is severely reduced. Transition structures were calculated for a model system in which the PMP group is replaced with a phenyl group (Figure 9). A large NBO delocalization energy of 4.07 kcal mol^{-1} is calculated for the 1,5-anti transition structure where the acetal oxygen is oriented toward the formyl hydrogen (**In-Anti**). A formyl hydrogen bond is not observed in the transition structure leading to the 1,5-syn adduct, presumably because the enforced clash between the cyclic acetal and the rest of the structure would be extremely unfavorable (Figure 10). Another 1,5-syn transition structure **(In-Syn)** was also located. This has no

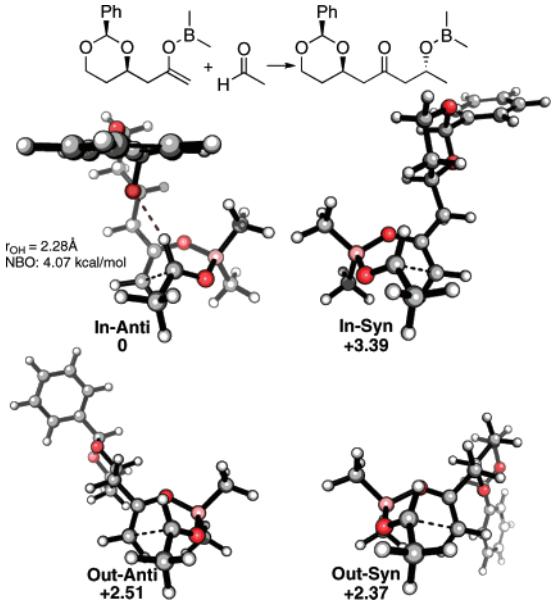
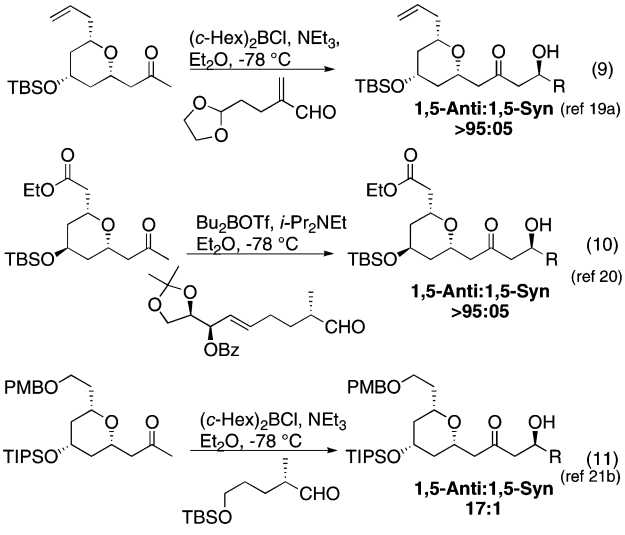


FIGURE 9. Aldol transition structures for a methyl ketone possessing a β-benzylidene acetal reacting with ethanal (relative energy in kcal mol^{-1} calculated in Et_2O).

C−H−O interaction and accordingly is much less favorable. The relative energies predict complete selectivity for the 1,5-anti adduct at −78 °C, which is in agreement with the observed ratio of 93:07.

***β*-Tetrahydropyran-Substituted Methyl Ketones** (Scheme 4, entry iv). In the Kozmin[19] (eq 9), Carreira[20] (eq 10), and Paterson[21] (eq 11) total syntheses of leucascandrolide, a β-tetrahydropyran-substituted methyl ketone is strategically used to produce the required 1,5-anti relationship of the natural product with high levels of diastereoselectivity (eqs 10 and 11).



The computed competing transition structures are shown in the Supporting Information, Figure S3. A very similar picture is seen as for PMP acetal protection, in which there is no internal hydrogen bond in the 1,5-syn transition structure, since the alkoxy group is part of a bulky ring. Formyl hydrogen bond formation is possible in the 1,5-anti transition structure since the tetrahydropyran ring is oriented away from the core structure.

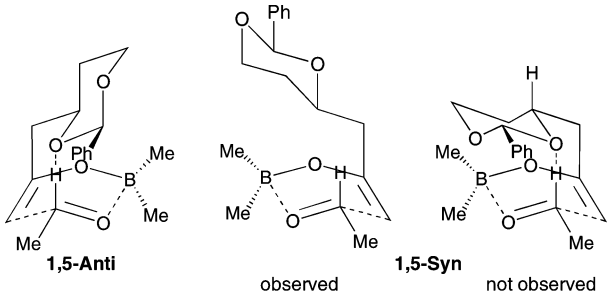


FIGURE 10. Model of competing transition structures where a β-benzylidene acetal is present. A formyl hydrogen bond is not observed in the 1,5-syn transition structure as there would be an extreme steric interaction between the acetal ring and one of the ligands.

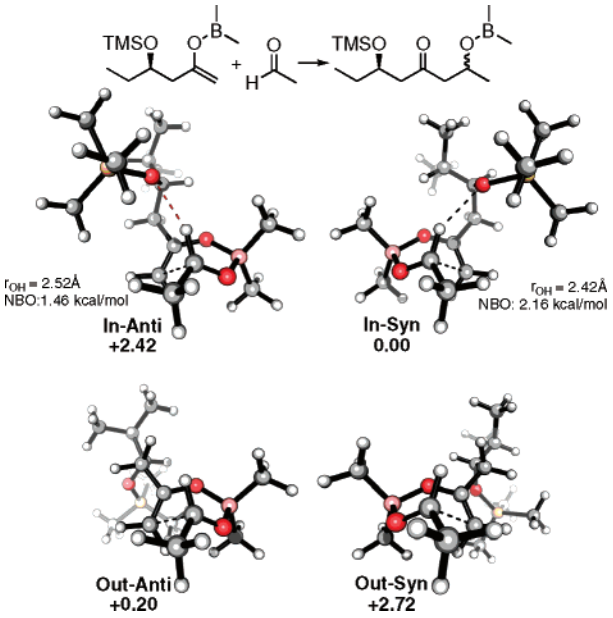
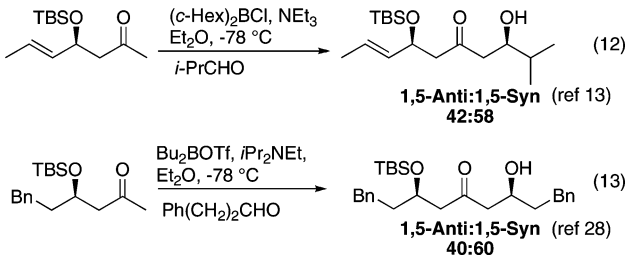


FIGURE 11. Aldol transition structures for a methyl ketone possessing a β-silyl ether (relative energy in kcal mol^{-1} calculated in Et_2O).

The relative energies predict a 1,5-anti to 1,5-syn ratio at −78 °C of 99:01, which is in agreement with the observed ratio of 93:07.

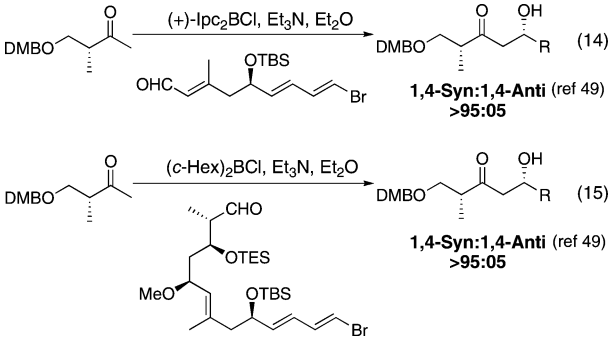
***β*-Silyl Ether-Substituted Methyl Ketones** (Scheme 4, entry v). In contrast to the behavior of PMB and PMP acetal protecting groups, silyl ethers show very little 1,5-induction, giving nearly equal amounts of the epimeric aldol adducts (eqs 12 and 13).



The transition structures were calculated for the model system shown in Figure 11, where a TMS protecting group has been used instead of the larger TBS group.

In this example there is no preference for the transition structures with a short C−H−O distance, with the **In-Anti** structure disfavored. Obviously the steric requirements of the silicon protecting group in proximity to the β-oxygen are much larger than the corresponding benzyl ether, and conformations where both β-substituents are in close proximity (as in **In-Anti**) involve significant clashes. Therefore, those transition structures where the silyl ether points away from the cyclic core will be favored. There is also a difference in electronic properties between the silyl- and benzyl ethers, demonstrated by the NBO calculations. The calculated C−H−O delocalization energy for **In-Anti** structure is just 1.46 kcal mol^{-1}, whereas values for the benzyl ether and benzylic acetal are 3.29 and 4.07 kcal mol^{-1}, respectively. However, significant delocalization into the silicon d-orbitals is observed. Therefore, a combination of large size and electron-deficient oxygen means that silyl groups favor a transition structure in which the enolate alkyl chain is oriented outward, since there is a large steric penalty and little electronic stabilization involved in pointing back inside. In the transition structures where the alkyl chain points away, there is little to choose between diastereomeric 1.5-anti and 1,5-syn structures. As a result the selectivity of β-silyl ethers is negligible. The uncorrected relative energies predict a 1,5-anti to 1,5-syn ratio at −78 °C of 37:63, which is in qualitative agreement with the overturning of selectivity relative to all other protecting groups investigated, and near quantitative agreement with the observed ratio of 40:60.

α-Chiral Methyl Ketones (Scheme 4, entry vi). Our formyl hydrogen bonding model also be used to rationalize the 1,4-syn aldol selectivity observed in the boron aldol reactions of α-substituted methyl ketones bearing a β-alkoxy group as developed in the Paterson group. In the total synthesis of dolastatin 19 two diastereoselective 1,4-syn aldol couplings are performed with a β-alkoxy methyl ketone bearing an α-methyl substituent (eqs 14 and 15).



Competing transition structures were calculated for a model system where a benzyl group replaces the dimethoxybenzyl (DMB) group, and the aldehyde partner is much simplified (Figure 12). Again, it is most favorable to orient the alkoxy group back in toward the formyl hydrogen to form a stabilizing C−H−O interaction.

In the diastereomeric transition structures leading to the 1,4-syn and 1,4-anti adduct the NBO delocalization energies are similar (3.89 and 3.65 kcal mol^{-1}, respectively). Here, the diastereomeric differentiation arises due to a steric interaction between the α-methyl group and the enolate double bond. In the transition structure leading to the 1,4-syn adduct, the enolate double bond is eclipsed by a hydrogen. However, the competing 1,4-anti transition structure experiences an unfavorable steric interaction as the α-methyl group eclipses the enolate double bond (Figure 13).

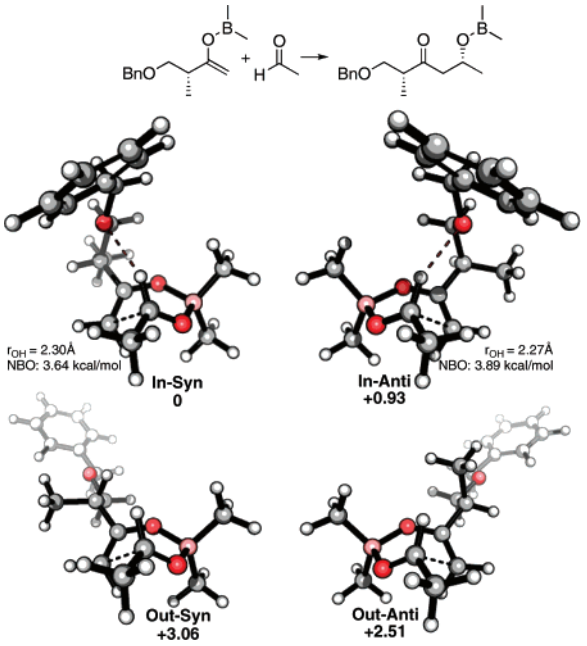
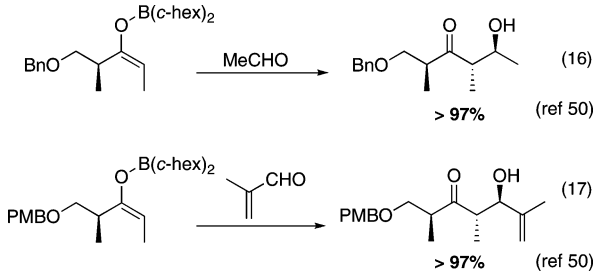


FIGURE 12. Competing transition structures in the aldol reaction of an α-substituted methyl ketone (relative energy in kcal mol^{-1} calculated in Et_2O).

The uncorrected relative energies predict a 1,4-syn to 1,4-anti ratio at −78 °C of 91:09, which is in excellent agreement with the observed ratios of >95:05. This formyl H-bonding model can also be extended to rationalize the higher levels of 1,4-syn selectivity obtained for the corresponding anti-aldol reaction of *E*-boron enolates. Adding a methyl substituent to the enolate double bond should lead to a greater steric clash in the 1,4-anti transition structure. This is exemplified by eqs 16 and 17, in which boron aldol reactions of α-chiral ethyl ketones with achiral aldehydes give the 1,4-syn adduct with extremely high levels of selectivity.[50]



Calculated B3LYP relative energies of competing boat A- and chair C-shaped aldol transition structures for the reaction of a *β*-methoxy *E*-boron enolate predict that the boat structure with a formyl H-bond is favored (see Table S2 and Figure S4 in the Supporting Information for full details of these calculations). Previous work has identified boat-shaped transition structures as important in rationalizing the stereochemical outcome in the reactions of *E*-boron enolates.[11] Figure 14 shows a model of the competing boat-shaped transition structures both stabilized by a formyl hydrogen bond, in which the 1,4-anti adduct is disfavored by an unfavorable steric interaction between the α-methyl group and the enolate *E*-methyl substituent.

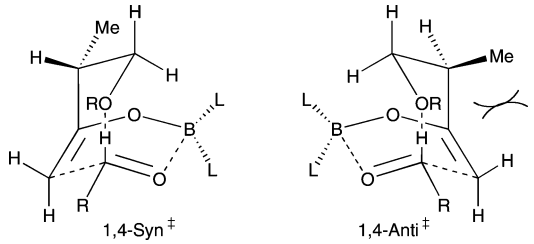


FIGURE 13. Models of the competing 1,4-syn and 1,4-anti transition structures.

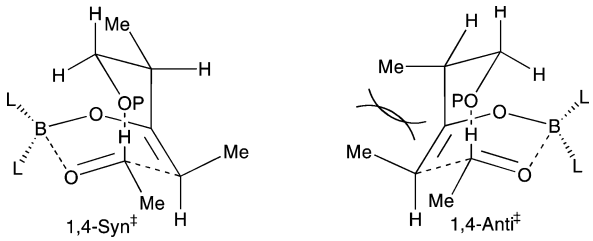


FIGURE 14. Models of the competing 1,4-syn and 1,4-anti boat-shaped transition structures for *E*-boron enolates.

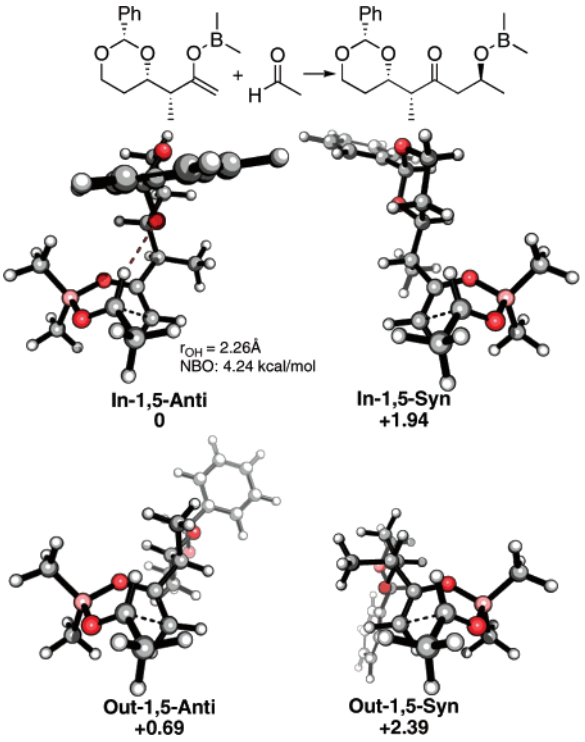
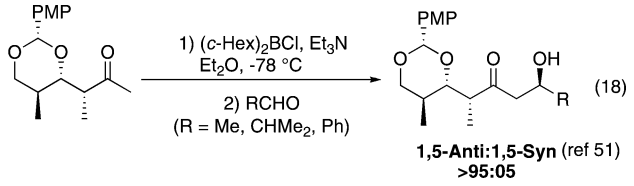


FIGURE 15. Aldol transition structures for a *β*-methoxy ketone (relative energy in kcal mol^{-1} calculated in Et_2O).

α,*β*-Chiral Methyl Ketones (Scheme 4, entry viii). It is often a challenge to predict the stereochemical outcome in aldol reactions where there are competing directing effects. For an α,*β*-chiral ketone what will happen when the 1,5-anti bias and 1,4-syn bias do not coincide? As a demonstration of the strength of the *β*-alkoxy stereocontrol, experimental results show that the effects of 1,5-anti induction play a dominant role and outweigh any influence from 1,4-syn induction due the presence of an α-methyl group (eq 18).

(50) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.
(51) Dias, L. C.; Baú, R. Z.; de Sousa, M. A.; Zukerman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325−4327.



(18)

The 1,5-anti transition structure avoids a steric interaction between the acetal ring and one of the ligands on boron, but suffers from the α-methyl group eclipsing the enolate double bond. Our previous calculations for a β-PMP acetal had already shown that the 1,5-Anti-In transition structure was more stable than 1,5-Syn-In by 3.4 kcal mol^{-1} (Figure 9), whereas an eclipsing α-methyl group was destabilizing by 0.9 kcal mol^{-1} (Figure 12). On this basis we expect that the 1,5-Anti-In transition structure should dominate, and our calculations show this to be the case. The uncorrected relative energies predict a 1,5-anti to 1,5-syn ratio at −78 °C of 99:01, which is in good agreement with the observed ratio of greater than 95:05 (Figure 15).

Conclusion

The boron aldol reaction between a series of β-alkoxy methyl ketones and ethanal has been investigated using density functional theory by means of B3LYP/6-31G** calculations. When methoxy, benzyl ether, and benzylidene acetal protecting groups are used, the transition structure favors an arrangement that allows the formation of a stabilizing formyl hydrogen bond between the alkoxy oxygen and aldehyde proton. The magnitude of this interaction has been evaluated using NBO perturbation theory analysis. Diastereomeric discrimination arises due to a steric clash between the β-alkyl substituent and one of the ligands on boron in the 1,5-syn transition structure.

For silyl ethers the preference for hydrogen bond formation is eroded in part due to the large size of the protecting group and in part due to an electron-deficient oxygen atom that donates electron density to the neighboring silicon atom. The reaction proceeds via a more open transition structure for which there is little diastereomeric differentiation between 1,5-anti and 1,5-syn adduct formation.

This model also rationalizes the excellent levels of 1,4-syn selectivity observed in the reactions of α-methyl boron enolates, and correctly predicts the outcome of competition between 1,4- and 1,5-stereoinduction: the latter dominates. An accurate model of asymmetric induction in boron enolates addition is critically important for predicting the outcome of complex aldol reactions, which can make or break a natural product synthesis. The prediction of diastereoselectivity from calculated Boltzmann factors in each example is in excellent agreement with experiment. A simple working model of the boat transition state gives the correct qualitative interpretation in all cases. This will be helpful in predicting the stereochemical outcome in future reactions with new substrates.

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Supporting Information Available: Cartesian coordinates of all transition structures discussed in the text, with gas-phase and solution-phase SCF absolute energies, zero-point energies and imaginary eigenfrequencies. This material is available free of charge via the Internet at http://pubs.acs.org.

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